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Common Genetic Variants in Candidate Genes and Risk of Familial Lymphoid Malignancies

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Summary

Familial aggregation, linkage, and case-control studies support the role of germline genes in the etiology of lymphoid malignancies. To further examine the role of genetic variation underlying susceptibility, we analyzed 1536 SNPs in 152 genes involved in apoptosis, DNA repair, immune response, and oxidative stress pathways among a unique sample of 165 unrelated familial cases including patients with chronic lymphocytic leukemia (CLL), Waldenström's (WM), and Hodgkin lymphoma (HL), and 107 spouse controls. We confirmed previous studies showing a polymorphism in the *IL10* promoter (rs1800890/-3575T>A) to be associated with non-Hodgkin lymphoma since we found this allele to be associated with both CLL and WM. We also confirmed the role of *IL6* variation to be associated with HL. Polymorphisms in the *TRAIL* gene were associated with both CLL and WM. Future replication and functional studies are needed to clarify the role of these genetic variants. Finally, our data further support the close association of WM and CLL.

Keywords

Candidate genes; association; familial; lymphoid malignancies; chronic lymphocytic leukemia; Waldenström's macroglobulinemia; Hodgkin lymphoma

Introduction

The etiology of lymphoid malignancies is poorly understood but studies support a role for immune-related and host genetic factors, in addition to environmental exposures. The risk of lymphoma is consistently increased among individuals with certain immune-related and inflammatory conditions, as well as persons who have undergone organ or allogeneic bone marrow transplantation (Alexander, *et al* 2007) (Goldin and Landgren 2009). A role for inherited genetic variation is supported by findings from high-risk families, case-control studies, and population-based familial aggregation studies (Goldin and Caporaso 2007). Using population-based registries of Scandinavia, we showed significantly increased risk of lymphoid malignancies among first degree relatives of cases (Goldin, *et al* 2005a, Goldin, *et al* 2004a,

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Goldin, *et al* 2004b, Landgren, *et al* 2006). Recently, we found that Waldenström's macroglobulinemia (WM)/lymphoplasmacytic lymphoma aggregates significantly in families and also co-aggregates with CLL and other NHLs (Kristinsson, *et al* 2008). Relatives of CLL patients are at significantly increased risk for developing WM in addition to being at increased risk for CLL (Goldin, *et al* 2009). Among high-risk CLL families that we have accrued in our clinical program, relatives with other lymphomas including NHL and WM have been observed (Goldin and Caporaso 2007, Ishibe, *et al* 2001, McMaster and Caporaso 2007, McMaster, *et al* 2007). One study found similar gene expression patterns in the tumors of CLL and WM patients. (Chng, *et al* 2006). These varied studies implicate shared genes and pathways across different lymphoid malignancies.

We and others have conducted gene mapping studies in high-risk families and have identified regions of the genome that are likely to contain susceptibility genes for HL (Goldin, *et al* 2005b), CLL (Goldin, *et al* 2003, Sellick, *et al* 2007, Sellick, *et al* 2005), and WM (McMaster, *et al* 2006). However, more research is needed to narrow these regions and identify candidate genes. A number of candidate genes and pathways have been suggested for NHL from case-control studies (Skibola, *et al* 2007). In particular, polymorphisms in *TNF* and *IL10* have been found to contribute to the risk of developing NHL in several studies (Lan, *et al* 2006, Purdue, *et al* 2007, Spink, *et al* 2006, Wang, *et al* 2006), and a polymorphism in the promoter region of *IL10* was found to be significant in a pooled analysis of 3000 NHL cases and 3000 controls (Rothman, *et al* 2006).

We used a unique resource of familial lymphoma patients to screen for associations of a large number of candidate genes with lymphoma. Consistent with the WHO classification, we use the term “lymphoma” broadly to include CLL. We investigated the effect of common genetic variants in 152 genes (1536 SNPs) using a custom designed Illumina panel. The genes were selected from pathways considered to be important in lymphoma pathogenesis including apoptosis, cell cycle, immune regulation, DNA repair and oxidative stress. The specific genes were chosen based on prior case-control studies, supporting evidence from gene expression and functional studies in the literature. We genotyped SNPs from these genes in 165 unrelated CLL, WM and HL patients from high risk families, along with 107 spouse controls from the same families. Familial cases are more likely to carry germ line variants leading to susceptibility (Houlston and Peto 2004). The goals of this study are to identify a small number of genes from this large set for further study and to replicate genes previously identified in the literature.

Material and Methods

Study populations

Our familial lymphoma patients have been described elsewhere (Goldin, *et al* 2003, Goldin, *et al* 2005b, Ishibe, *et al* 2001, McMaster, *et al* 2007, McMaster, *et al* 2006). In brief, the Genetic Epidemiology Branch of the National Cancer Institute, NIH, has been accruing families with two or more patients affected with the same type of lymphoma including CLL, WM, HL, and other NHLs. We evaluated all affected individuals and informative relatives either at the NIH Clinical Center or in the field and obtained biospecimens, all available medical records, pathology reports, and pathology specimens. Original pathology material and reports for HL patients were also reviewed by the National Cancer Institute Laboratory of Pathology. Families have been followed longitudinally, and the diagnostic status of individuals has been regularly updated. Blood samples were collected from each individual (all were Caucasians). Genomic DNA was extracted from cryopreserved lymphocytes using standard methods. All samples were coded and stored at -80° until used. Our current study includes 165 unrelated patients (44 CLL, 71 WM, 50 HL) and a control group of 107 unrelated spouses from these

high-risk families. This study was conducted under institutional review board approval, and all subjects gave informed consent.

Candidate gene selection

We selected 152 candidate genes (Table 1) based on published and unpublished data from case-control studies. Major categories of candidates included apoptosis/cell cycle, DNA repair, immune response, TH1/TH2, TNF/NFKB, and oxidative stress. TagSNPs were selected from the designable set using the program Tagzilla (http://tagzilla.nci.nih.gov) with the restriction that the linkage disequilibrium (LD) between selected SNPs measured by r^2 must be less than 0.8 and the minor allele frequency (MAF) must be greater than 5% based on HapMap CEPH (CEU) genotype data. The final set of 1536 SNPs was genotyped using the Illumina GoldenGate Oligo Pool Assay (OPA) on an Illumina BeadStation 500 GX (Illumina Inc., San Diego, CA) (http://www.illumina.com).

Quality assessment

Upon receipt, the OPA was genotyped on a validation set consisting of 191 DNA samples, including HapMap CEU trios and 102 samples from SNP500 Cancer (Packer, *et al* 2006). Eight sets of duplicate DNA samples were implemented across plates for genotyping quality control. Data from each of the 1536 SNP assays were visually inspected using Illumina's Bead Studio software to detect clustering failures. Completion rates were calculated for each assay per sample and per informative locus (excluding assays that failed to cluster, as described above). Concordance per assay was determined by comparing NCI Core Genotyping Facility (CGF)-generated genotypes with those reported by the HapMap for the same CEU samples.

Statistical Analysis

We tested all SNPs for Hardy-Weinberg Equilibrium (HWE) in cases and controls separately using the Haploview program (Barrett, *et al* 2005). SNPs were excluded if the HWE p-value was $<3\times10^{-5}$ (Bonferroni correction for 1536 SNPs at p=0.05) for controls. Linkage disequilibrium was examined in our samples to detect any residual correlations among SNP pairs. We deleted SNPs with $r^2 > 0.8$ with another SNP (retaining the SNP with higher minor allele frequency) based on our samples. Allelic association, genotypic association and trend test for single SNPs were tested using the SAS Genetics program (SAS Institute) for each lymphoma subtype separately.

We screened for genes within each patient subgroup (CLL, WM, and HL). For these analyses, we present results for genes with 3 or more SNPs having nominal p-values <0.05 using the trend test. For all genes that met this initial screening criterion, the false discovery rate (FDR) was calculated to correct for multiple comparisons based on the number of genotyped SNPs in each gene. FDR was set to ≤ 0.2 (Benjamini, *et al* 2001, Benjamini and Hochberg 1995, Storey and Tibshirani 2003), the goal being to select the best genes for further study. For SNPs that were found to be significant in more than one disease, we used logistic regression (correcting for gender) to compute the odds ratios and 95% confidence intervals.

Results

Quality Control Analyses

Among 1536 genotyped SNPs, 46 SNPs (3%) failed genotyping, and 1 was not polymorphic and four exceeded the Hardy-Weinberg Equilibrium threshold in controls. The completion rate for the remaining SNPs and samples was greater than 99.8%.

Association Analyses

Table 2 shows the screening results for CLL, WM, and HL separately. For each gene meeting our screening criteria, we show the number of significant SNPs and the total number of SNPs tested. The nominal p-values for associated SNPs are listed in the supplementary table. As the table shows, most of the genes met our criteria for further study based on FDR correction for multiple testing. Four genes were associated with both CLL and WM (*BCL2, IL10, TRAIL and TRAILR1*). We focused further on the *IL10* and *TRAIL* genes as there were SNPs overlapping both CLL and WM. For these SNPs, we computed odds ratios (ORs) under an additive model using the common allele as the referent in logistic regression. Table 3 shows that the odds ratios of the two SNPs in *IL10* (rs1800890 and rs17015865) were in the same direction for both CLL and WM. For the *TRAIL* gene, one SNP showed protective effect in both CLL and WM; and for the other, the effects were opposite. Table 2 also shows that six genes were associated with HL. All of them except BCL2 and WRN met criteria for further study after correction of multiple comparisons by controlling FDR. *IL6* polymorphisms were associated with both HL and WM but they were not the same SNPs.

Discussion

This is the first large scale study of candidate genes for association involving a unique set of diverse familial lymphoid malignancies and several findings are noteworthy. SNPs in *BCL2* were associated with all three diseases. Although BCL2 is a strong candidate gene, there were no overlapping SNPs among the three lymphomas. Since more than 50 SNPs were tested, chance is a plausible explanation for the findings observed. We found that SNPs in *IL10* were significantly associated with both WM and CLL patients. *IL10* is involved in several pathways that are potentially relevant for lymphomagenesis. The rs1800890 SNP in the promoter of *IL10* (-3575T>A) has previously been found to be associated with NHL in case-controls studies (Lan, *et al* 2006, Rothman, *et al* 2006). In our study, the same variant allele was associated with both CLL and WM. In addition, *IL10* is close to a linkage peak on chromosome 1 that we previously identified in a genome wide linkage study of families at high risk for WM (McMaster, *et al* 2006). Our findings of SNPs associated with similar ORs in CLL and WM are consistent with the familial aggregation and gene expression studies and support a close biological relationship between them.

SNPs in *IL6* were also associated with HL and WM. *IL6* is involved in lymphocyte differentiation and is upregulated in HL (Gutierrez, *et al* 2007, Nagel, *et al* 2005, Vener, *et al* 2000) (Nagel, *et al* 2005, Vener, *et al* 2000). A promoter polymorphism in *IL6* (rs1800795,174G>C) was reported to be associated with HL (Cordano, *et al* 2005, Cozen, *et al* 2004). However, this SNP was not genotyped either in our sample or the HapMap samples so we do not know if it is in linkage disequilibrium with our associated SNPs. *IL6* is also near a linkage peak on chromosome 7 that we identified in families at high risk for HL (Goldin, *et al* 2005b). *IL6* is a strong candidate for WM as well since studies have also shown upregulation of IL6 levels in WM tumors. (Chng, *et al* 2006, Gutierrez, *et al* 2007).

We identified several other genes that are promising but require additional replication. The associations of *FASLG*, *TRAIL* and *TRAIL-receptor 1* with CLL are noteworthy as these genes are all involved in the extrinsic apoptosis pathway and prior studies show altered function in CLL B-cells (Dicker, *et al* 2005, Kaufmann and Steensma 2005, Scholz and Cinatl 2005). One of the SNPs in the *TRAIL* gene also showed similar ORs in both CLL and WM. The possible associations of both the *IL1R1* and *IL4R* genes with HL are noteworthy. The binding of *IL1R1* to its agonist activates *NFKB*, which is constitutively expressed in HL cells (Stylianou and Saklatvala 1998). *IL4R* has been found to be highly expressed in Hodgkin-Reed Sternberg cells and is being studied as a molecular target for drug development in HL (Kawakami, *et al* 2005).

Our study is limited by sample size but we selected familial lymphoma patients (including the rare subtype WM), which increases the power of association studies. Houlston and Peto (Houlston and Peto 2003) have shown that collecting cases with two or more affected relatives increases the power to identify rare low penetrance variants. They showed that for cases with two additional affected relatives, the number of cases required detecting an effect with OR of 2.0 with 1% population prevalence is four- to five-fold reduced compared to using unselected cases.

It is likely that multiple genes are involved in susceptibility to familial lymphoid malignancies. A previous genome-wide linkage scan in high risk CLL families found evidence for multiple susceptibility gene regions (Sellick, *et al* 2007). A recent genome-wide association study of CLL cases compared to controls also suggested an underlying multiple-gene model where six risk loci were identified (*IRF4, PRKD2, SP140, GRAMD1B, BCL2L11*) (Di Bernardo, *et al* 2008). In our study, 2 SNPs in two of those genes were also associated with CLL, although they were not the same SNPs. They were rs11681263 in *BCL2L11* on chromosome 2 with p=0.01, and rs6900384 in *IRF4* on chromosome 6 with p=0.03 (data not shown).

In summary, our study has replicated a reported association of *IL10* SNPs with lymphoid malignancies and an association of the *IL6* gene with HL. The *TRAIL* gene findings are also promising given that both CLL and WM were associated with the same SNPs. Our findings also support other data suggesting a close biological relationship between CLL and WM. Future genome-wide association studies and linkage studies are needed to confirm the findings and further clarify the role of genetic variants in relationship to risk of developing lymphoid malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Candidate genes and pathways

Pathway	Genes
Apoptosis/cell cycle	*AICDA, BAX, BCL2, BCL2A1, BCL2L1, BCL2L2, BCL2L10, BCL2L11(BIM), BCL6, BCL7A, BCL7C, BCL10, CASP1, CASP14, CASP4, CASP5, CASP6, CASP7, CASP8AP2, CASP9, CCND1, LMO2, MYC, PIM1, RIPK1, RIPK2, TP53, TP53I3*
DNA Repair	*BLM, BRCA1, BRCA2, ERCC1/2, ERCC3, ERCC5, ERCC6, LIG1, LIG3, LIG4, MDM2, MRE11A, NBN, PRKDC, RAD50, RAD51, RAD54L, RAG1/2, WRN, XRCC1, XRCC2, XRCC3, XRCC4*
Immune Regulation	*CD4, CD79A, CD79B, FCGR2A, ICAM1, IL12A, IL15, IL1A, IL1B, IL1R1, IL1R2, IL1RN, IL2, IL5, IL6, IL6R, IL6ST, IL8, IL8RA/RB, JAK3, TLR1, TLR10, TLR2, TLR4, TLR6*
TH1/TH2	*CD28, CD5, CD81, IL10, IL10RA, IL10RB, IL12B, IL12RB1, IL12RB2, IL13, IL18, IL19, IL4, IL4R, IL9*
TNF/NFKB	*CASP2, CASP3, CASP8, CD40, CFLAR, CHUK, FADD, FAS, FASLG, IKBKB, IRF4, NFKB1, NFKB2, NFKBIA, NFKBIE, NFRKB, REL, RELA, RELB, RPL13P2, TANK, TNF/LTA, TNFRSF10A/B/C/D(TRAILR1-R4), TNFRSF12A, TNFRSF13B, TNFRSF13C, TNFRSF14, TNFRSF17, TNFRSF1A, TNFRSF1B, TNFRSF25, TNFRSF4, TNFRSF7(CD27), TNFRSF8, TNFRSF9, TNFSF10(TRAIL), TNFSF13(APRIL), TNFSF14, TNFSF18, TNFSF4, TNFSF7(CD70), TNFSF8, TNFSF9, TRADD, TRAF2, TRAF5, TRAF6, VCAM1*
Oxidative Stress	*GPX1, GPX2, GPX3, GPX4*
Angiogenesis	*VEGF*

Table 2

Genes with three or more significant SNPs in lymphoma subtypes

subtype	gene	associated SNPs with p<0.05 (n)	Total SNPs (n)	meet criteria for following up after FDR correction
CLL	*BCL2*	3	56	No
	FASLG	5	11	Yes
	TNFSF7	3	14	Yes
	IL10	3	13	Yes
	TRAIL	3	17	Yes
	TRAILR1	4	16	Yes
WM	*BCL2*	4	56	No
	BCL6	4	10	Yes
	IL10	6	13	Yes
	IL6	3	15	Yes
	IL8RA	3	4	Yes
	TRAIL	4	17	Yes
	TRAILR1	3	16	No
	WRN	4	18	Yes
HL	*BCL2*	4	56	No
	IL1R1	5	16	Yes
	IL4R	6	18	Yes
	IL6	4	15	Yes
	LMO2	3	20	Yes
	WRN	3	18	No

* CLL=chronic lymphocytic leukemia, WM=Waldenström's macroglobulinemia, HL= Hodgkin lymphoma

Table 3

Odds ratios of *IL10* and *TRAIL* SNPs in CLL and WM

			CLL				WM			
Gene	**SNP**	**genotype**	**case**	**control**	**OR (95% CI)**	**P****	**case**	**control**	**OR (95% CI)**	**P****
IL10	rs1800890	TT	19	33	ref		31	33	ref	
		AT	16	48	0.55 (0.24-1.24)	0.15	30	48	0.58 (0.29-1.16)	0.12
		AA	4	21	0.30 (0.09-1.04)	0.06	6	21	***0.26 (0.10-0.77)***	***0.01***
		trend			***0.57 (0.32-0.99)***	***0.04***			***0.54 (0.33-0.87)***	***0.01***
	rs17015865	CC	27	54	ref		46	54	ref	
		CT	11	38	0.56 (0.25-1.28)	0.17	19	38	0.56 (0.28-1.11)	0.10
		TT	1	10	0.19 (0.02-1.60)	0.13	2	10	***0.19 (0.04-0.96)***	***0.04***
		trend			***0.51 (0.27-1.00)***	***0.05***			***0.51 (0.30-0.88)***	***0.02***
TRAIL	rs3136597	AA	27	51	ref		44	51	ref	
		AC	12	43	0.53 (0.24-1.16)	0.11	20	43	0.53 (0.27-1.04)	0.07
		CC	0	8	N/A	N/A	3	8	0.55 (0.13-2.30)	0.41
		trend			***0.43 (0.21-0.88)***	***0.02***			0.62 (0.36-1.06)	0.08
	rs2241063	AA	16	63	ref		51	63	ref	
		AC	19	35	2.14 (0.98-4.68)	0.06	15	35	0.50 (0.24-1.03)	0.06
		CC	4	4	4.27 (0.93-19.55)	0.06	1	4	0.27 (0.03-2.56)	0.25
		trend			***2.06 (1.12-3.78)***	***0.02***			***0.51 (0.27-0.95)***	***0.03***

*CLL=chronic lymphocytic leukemia, WM=Waldenström's macroglobulinemia

**adjusted for gender